22. (Three Times Amended) A method of inserting a heterologous gene coding sequence into an endogenous gene in a mouse embryonic stem cell genome and expressing said heterologous gene coding sequence, comprising the step of transforming the mouse embryonic stem cell with a DNA construct, wherein the DNA construct lacks a promoter, and (ii) comprises the sequence:

5' A-P-B-Q-C 3'

in which

P is an internal ribosome entry site (IRES),

Q is the heterologous gene sequence, and

A, B and C are, separately, optional linker sequences;

wherein the DNA construct further comprises a polyadenylation signal at the 3' (downstream) end of Q and a splice acceptor site located 5' (upstream) of Q.

28. (Twice Amended) A mouse embryonic stem cell comprising a heterologous gene coding sequence inserted by the method of Claim 22.

29. (Twice Amended) A descendant of the mouse embryonic stem cell according to Claim 28, wherein the descendant has inherited the inserted heterologous gene coding sequence.

30. (Amended) A mouse comprising a cell according to Claim 29.

31. (Amended) A descendant of a mouse according to Claim 30, wherein the descendant has inherited the inserted heterologous gene coding sequence.

32. (Three Times Amended) A DNA construct comprising the sequence:

5' A-P-B-Q-C 3'

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in which

P is an internal ribosome entry site (IRES),

Q is a [the] heterologous gene sequence, and

A, B and C are, separately, optional linker sequences;

wherein the DNA construct further comprises a polyadenylation signal at the 3' (downstream) end of Q and a splice acceptor site located 5' (upstream) of Q.

34. (Twice Amended) A DNA construct according to Claim 32 in which the heterologous gene sequence additionally codes for a selectable marker to facilitate selection of cells containing a heterologous gene that has been inserted into an endogenous gene.

REMARKS

Applicants have canceled claims 43-46 and amended claims 22, 28-32, and 34. The specification has been amended to insert a Sequence Listing and to correct a minor informality. All of the amendments are supported by the specification and claims as filed and do not add new matter. None of the amendments should be construed as abandoning any subject matter. Applicants specifically reserve the right to prosecute such subject matter in a later filed application.

Sequence Compliance

In order to comply with the nucleotide sequence listing rules, 37 C.F.R. §§ 1.801-1.825, and in lieu of filing a computer readable form in this application, applicants make reference to the Sequence Listing and computer readable submission in U.S. application Serial No. 08/537,765, from which this application claims priority. The

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